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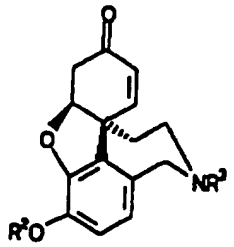
(54) Title: PROCESS FOR THE PREPARATION OF GALANTHAMINE AND ITS DERIVATIVES

(57) Abstract

A process for preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R^1, R^2, R^3 and R^4 are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprises mixing with a plant extract an oxidative cyclisation precursor of the said compound.



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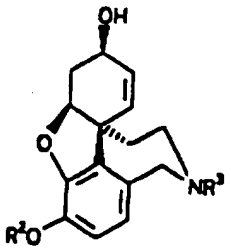

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PROCESS FOR THE PREPARATION OF GALANTHAMINE AND ITS DERIVATIVES

Field of the Invention

The present invention relates to a process for producing galanthamine and/or its derivatives from plant extracts.

Background of the Invention

Galanthamine (and its derivatives) are useful compounds for the treatment of Alzheimer's disease and related illnesses. Currently galanthamine, nor-galanthamine and the oxidised precursors thereof, narwedine and nor-narwedine, are usually obtained by extraction from particular types of bulbs, such as daffodils or snowdrops. The yields of these extractive procedures are extremely low, resulting in product(s) which are expensive and in short supply.

Studies have shown that the biosynthesis of such compounds probably proceeds by a pathway similar to that shown in Scheme 1 below, where the key step is an oxidative cyclisation. These studies have also indicated that when the cyclisation precursor lacks a methyl group on the amine nitrogen (i.e. R = H) the biosynthesis to narwedine and galanthamine is disfavoured, and instead proceeds down other pathways, e.g. to pyrrolo(de)phenanthridine and ethanophenanthridine alkaloids (see Barton and Kirby, J. Chem. Soc. (1961) 806 and Fuganti et al, Tetrahedron Lett. (1974) 2261).

Summary of the Invention

According to the present invention, a process for preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R^1, R^2, R^3 and R^4 are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprises mixing with a plant extract an oxidative cyclisation precursor of the said compound. All formulae are depicted below.

Surprisingly, the process of the present invention is capable of achieving higher yields of the desired compounds

than simple extraction from bulbs, and has the further advantage of its own simplicity. The process is particularly useful for the preparation of such compounds in optically-enriched form, more particularly (-)-galanthamine or (-)-narwedine.

Description of the Invention

Whether the process of the invention results in an optically-enriched or racemic form of a desired compound may depend upon the choice of the precursor to be mixed with the plant extract. Typically, however, an optically-enriched form is achieved. This is particularly advantageous when the product is (-)-galanthamine, or a derivative thereof, on account of its therapeutic activity. However, if the product is racemic or optically-enriched narwedine, or a derivative thereof, it can be readily converted to optically-enriched, eg. (-), galanthamine by a process such as that described by Shieh et al, J. Org. Chem. (1994) 59: 5463.

By optically-enriched typically we mean mixtures of enantiomers having an enantiomeric excess of at least 50%, and more typically at least 80%, or 90% or higher, thereby including single enantiomer form.

The groups R^1 to R^4 have been defined above, and typically include up to 20 carbon atoms. The preferred precursor compound for the preparation of (-)-galanthamine has surprisingly been found to be a secondary amine having the formula (3), below, in which the nitrogen atom is unsubstituted, ie. R^3 = H, contrary to what is disclosed in the prior art discussed above. Particularly preferred precursor compounds are of formula (3) in which R^1 = R^3 = R^4 = H and R^2 = alkyl, preferably methyl.

The plant extract is typically derived from daffodils or snowdrops, although other plants may give suitable extracts, and is preferably derived from the bulb of the plant. The extract is typically used in fragmented form, for instance by crushing with a pestle and mortar, and is then suspended in a liquid medium. Typically, the liquid

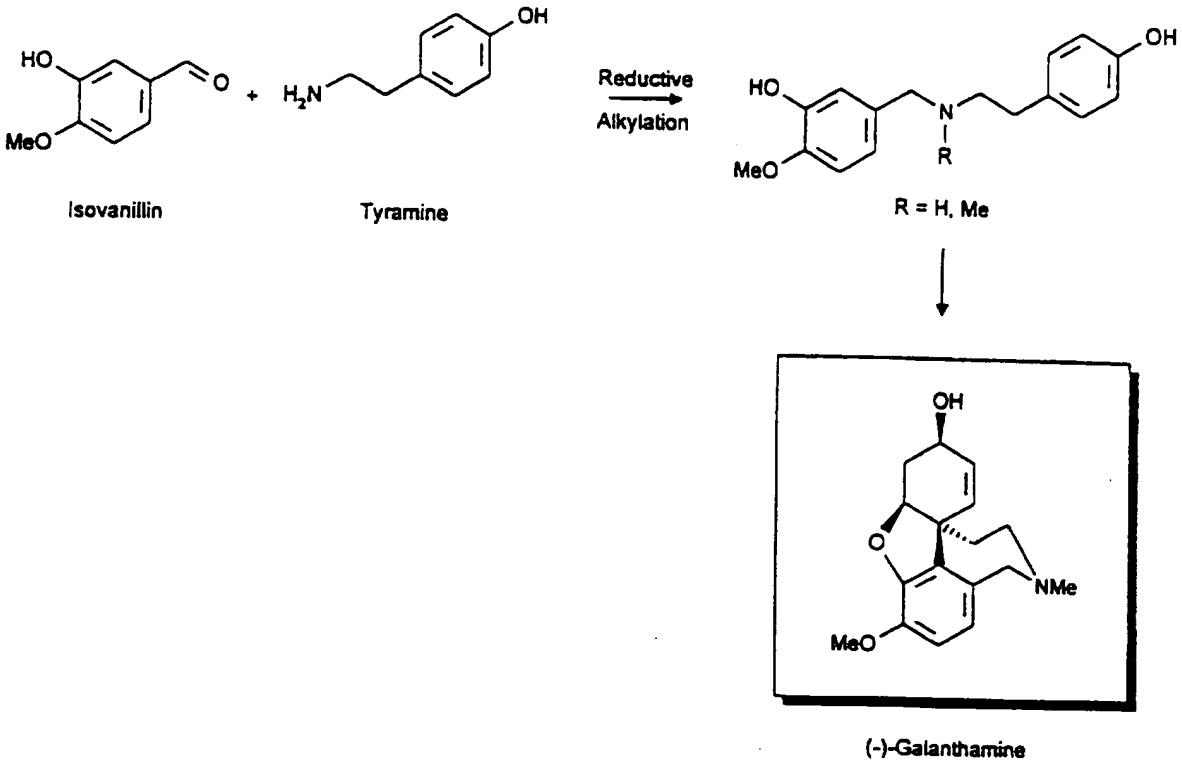
medium comprises an aqueous buffer, optionally including an additive such as an organic solvent or a surfactant. The precursor compound is then added to the liquid mixture, and preferably stirred for a period. The mixture is then extracted in a conventional manner.

The present invention is now further illustrated by the following Example.

Example

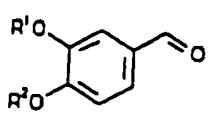
Daffodil bulbs which had been stored in a refrigerator were allowed to warm to room temperature over night. The bulbs were crushed with a pestle and mortar and a 1 g sample of this material was stirred with 10 mg of a secondary amine of formula (3) below, in which $R^1 = R^3 = R^4 = H$ and $R^2 = Me$, in aqueous phosphate buffer (20 ml) and ethnol (10 ml) for 18 hours. The mixture was then extracted with ethyl acetate and then concentrated in vacuo. Gas chromatographic analysis of the residue indicated that three times the amount of (-)-galanthamine was produced in comparison with a control reaction, which was run under identical conditions but without the addition of the amine (3).

Scheme 1



Isovanillin Tyramine (-)-Galanthamine

Formulae



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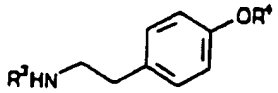

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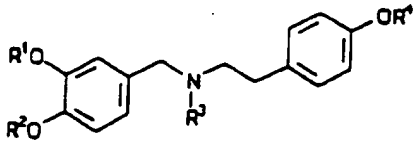

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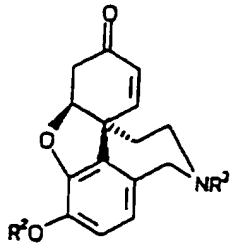

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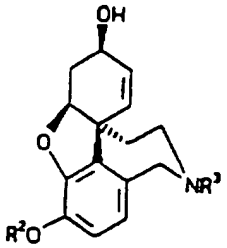
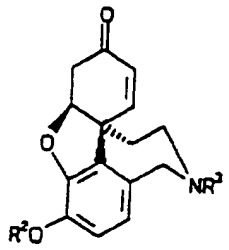


(5)

CLAIMS

1. A process for preparing a compound having a formula (4) or (5), in either optically-enriched or racemic form, wherein R^1, R^2, R^3 and R^4 are independently selected from hydrogen, alkyl, aryl, alkaryl, aralkyl and acyl groups, comprising mixing with a plant extract an oxidative cyclisation precursor of the said compound.



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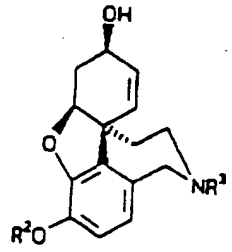

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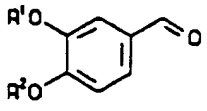
2. A process according to claim 1, wherein the precursor has a formula selected from (1) to (3).



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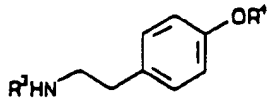

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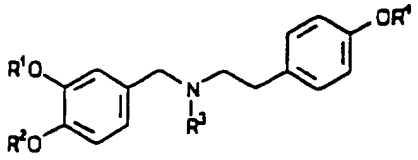

(3)

3. A process according to claim 1 or claim 2, which is for preparing the said compound in optically-enriched form.

4. A process according to claim 3, which is for preparing the said compound with the stereochemistry shown.

5. A process according to claim 4, which is for preparing (-)-galanthamine.

6. A process according to claim 5, wherein the precursor has the formula (3) in which R^3 = H.

7. A process according to claim 6, wherein in the precursor R^1 = R^4 = H and R^2 = alkyl.

8. A process according to claim 7, wherein R^2 = methyl.

9. A process according to any preceding claim, wherein the mixing is carried out in a suitable liquid medium.

10. A process according to any preceding claim, wherein the plant extract is derived from daffodils or snowdrops.

11. A process according to any preceding claim, wherein the extract is derived from the bulb of the plant.

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/GB 96/02335

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/10 C12P17/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	APPLIED MICROBIOLOGY BIOTECHNOLOGY, vol. 23, no. 3-4, 1986, pages 206-210, XP000571729 G. SPASSOV ET AL: "Microbial transformations of galanthamin-precursors" see page 206 ---	1
A	LA CHIMICA E L'INDUSTRIA, vol. 51, no. 11, 1969, pages 1254-1255, XP000571896 C. FUGANTI: "Biosynthesis of galanthamine: Feeding experiments in Leucojum aestivum (Amaryllidaceae)" see page 1254 --- -/--	1

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	TETRAHEDRON LETTERS, no. 26, 1974, OXFORD GB, pages 2261-2264, XP000608475 C. FUGANTI ET AL: "Further information on the origin of the aromatic, C-6, C-1 unit of the Amaryllidaceae alkaloids" cited in the application see page 2261 ---	1
A	J. HETEROCYCLIC CHEM., vol. 25, - 1988 pages 1809-1811 , XP000562834 J. SZEWCZYK ET AL: "An improved synthesis of Galanthamine" see page 1809 -----	1